

a 'spacer' heterocyclic group between the retinoic acid derivative and the glucosyl group." The importance of the spacer group as an essential feature of the instant invention and its critical physiological function is described on pages 2-4 of the instant specification. The spacer group makes possible an enzymatic double hydrolysis, first of β -glucocerebrosidase type and then of esterase type, through which a delayed release of the retinoic active agent is achieved without an accumulation effect in the various layers of the skin. Moreover, at pages 21 and 22 of the Specification, the applicants have, in fact, demonstrated the criticality of this structure. When compared to complexes not possessing the instant inventive structure, the instant compounds were demonstrated to exhibit lower rates of hydrolysis which enables the effect of the substance to be obtained for a prolonged time. Thus, the applicants have demonstrated critical activity and it is up to the Office to rebut this demonstration. The applicants submit that the Office has provided no teaching which would suggest that substances without the linker group would function as described and enabled in the specification.

It is the position of the Office that the "lower alkyl groups" of the lower alkyl glucoside complexes disclosed in Bollag, et al. are equivalent to the linker groups of the instant invention. The applicants submit that the lower alkyl glucoside complexes disclosed in Bollag, et al. **do not** refer to compounds having a lower alkyl group as a linker between the sugar residue and the retinoic acid derivative. Based on the examples disclosed in Bollag, et al., as well as the nomenclature used, the only lower alkyl groups disclosed refer to substituents on positions of the sugar residue other than the point of attachment between the sugar residue and the retinoic acid derivative. Additionally, the method of synthesis disclosed in Bollag, et al. (i.e., coupling of one or more of the free hydroxyl groups or free amino groups of the sugar residue with a reactive

derivative of retinoic acid) is not amenable to the synthesis of compounds in which the retinoic acid derivative is attached to the sugar residue via an alkyl linker. Therefore, Bollag, et al. may not be relied upon for teaching an alkyl linker group.

Moreover, it is the position of the Office that the process of making retinoids wherein a sugar is linked "ester-wise" to a retinoic acid derivative is within the teaching of von Deesen, et al.. However, von Deesen, et al. disclose glycosides of retinol which are linked via an ether linkage and ***specifically lack*** the instant ester linkage between the sugar residue and the retinoic acid derivative. Thus, the Office has made its argument on a misinterpretation of the prior art disclosure. In that von Deesen, et al. do not teach structurally or synthetically relevant subject matter, its teaching may not be considered relevant to the instant enquiry. The applicants submit that there is no motivation to combine the two references and therefore, the neopentylglycoacetal intermediate which is cited by the Examiner and disclosed in von Deesen, et al. is simply that, a synthetic disclosure which has no bearing on the instant invention.

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To summarize, the Office admits that Bollag, et al. discloses no linker group, but the Office maintains that since Bollag, et al. discloses alkyl substitution, this alkyl substitution would be possible at the position of the linker group. This is neither supported by the reference nor understood by those skilled in the art. In any event, the Office concludes that "alkyl linker groups" are obvious based on Bollag, et al. The Office further assumes that these presumed "alkyl linker groups" are equivalent to the unique heterocyclic linker groups of the instant invention. The applicants submit that the disclosure of Bollag, et al. does not

support the Office presumption that the disclosed alkyl groups make "alkyl linker groups" obvious, much less that these alkyl groups are equivalent to the instant heterocyclic linker groups. The Office further cites von Deesen, et al. to support the Office conclusion that the instant glucosyl ester-wise complexes of retinoic acid would be obvious to those skilled in the art; however, von Deesen, et al. discloses compounds with an ether linkage. The Office has provided no teaching for the motivation to combine these two references. Moreover, even if the Office were to have demonstrated some equivalence between what it presumes to be teaching for alkyl linker groups and the instant heterocyclic linker groups, the applicants have demonstrated the critical physiological function of the claimed heterocyclic linkers by showing that the instant compounds exhibit lower rates of hydrolysis when compared to other similar complexes. This lower rate of hydrolysis enables a prolonged effect of the substance, and thereby distinguishes the instant invention from even the most expansive interpretation of the prior art.

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Accordingly, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By:


G. PATRICK SAGE

Dated: December 22, 2003

Customer No.: 25,666

500 Columbia Plaza

350 East Michigan Ave.

Kalamazoo, MI 49007-3856

(269) 382-0030

Enclosure: Postal Card Receipt

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